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(54) Title: TRANSDERMAL PATCH

(57) Abstract

The present invention provides for a patch suitable for administering a medicinal agent to a subject that includes a removable liner forming a substrate, and a composition layer that includes a therapeutically effective amount of the medicinal agent in admixture with a pharmaceutically acceptable polyvinyl compound, such as polyvinyl pyrrolidone, and a plasticizer. The composition layer secures the patch to the subject to allow for the topical administering of the medicinal agent to the subject. The patch of the present invention further includes a backing layer and an adhesive layer for securing the backing thereto.

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# TRANSDERMAL PATCH

## Background of the Invention

The present invention relates to a drug delivery system, and more particularly, relates to a method and device for delivering a drug to a subject to effect a biological change.

Conventional devices that deliver drugs through intact skin, namely the epidermis, for absorption into the body and the systemic circulatory system have been known for some time. Such devices can be referred to as transdermal drug delivery devices or dermal compositions.

The purpose of such devices is to dispense a drug at a controlled rate by delivering the drug to the subject in a biologically effective and efficient manner. A typical prior art system includes a selected drug contained within a polymer matrix. The drug diffuses out of the matrix at a selected, controlled rate. These systems, however, are complicated to manufacture since they require a rate limiting means or structure to be disposed within the device to effectively and efficiently dispense the drug.

Of increasing interest are transdermal drug delivery devices in which the drug is incorporated into a pressure sensitive adhesive, which serves not only to carry the drug, but to attach the device to the skin. The introduction of a drug into a pressure sensitive adhesive, which is distinct from carrying the drug in a separate structure of the device, results in a variety of delivery and adhesion problems. These problems vary with, among other things, the nature of the polymers forming the pressure sensitive adhesive, the type and amount of drug, the type and amount of other ingredients in the system, such as fillers, and the required conditions of use. Typically, the transdermal devices must be strong enough to adhere to the wearer for a time sufficient to dispense the drug to produce a biological change. Otherwise, the individual may not receive the proper or prescribed amount of the drug.

Other conventional methods of introducing a drug into the blood stream are by direct injection and by oral administration. The direct injection technique typically subjects the patient to trauma involved with the penetration of a needle into intact skin. These traumas can be avoided by employing other non-invasive techniques, such as the use of topically or orally administered non-invasive devices. In the latter case, the drug is absorbed through a membrane or structure which contains the drug. According to this technique, the drug is introduced into the oral cavity by devices including sublingual tablets buccal tablets, ointments, gels and other sublingual devices.

A drawback of sublingual tablets are that they have relatively small surfaces in which to effect the transmission of the drug through the mucosal membrane.

Furthermore, in the case of sublingual location, the tablet when placed within the oral cavity tends to cause salivation, and by reason of the additional fluid and the position of the tablet in the mouth, is likely to lead to swallowing of at least a portion of the drug. Furthermore, sublingual tablets as well as buccal tablets notably induce the subject to crunch and to swallow the tablet because of the associated feeling of a foreign body within the oral cavity. Moreover, these types of tablets are difficult to retain in the mouth for extended periods of time.

Hence, there still exists a need in the art for a suitable device to administer one or more selected drugs to the epidermis or the oral mucosa of the subject to effect a biological change.

## Summary of the Invention

The present invention is based, at least in part, on the discovery that a patch containing a medicinal agent and a polyvinyl adhesive compound can be administered to a subject to effect a biological change. The present invention provides a patch suitable for administering a medicinal agent to a subject that includes a removable liner forming a substrate, and a composition layer that includes a therapeutically effective amount of the medicinal agent and a pharmaceutically acceptable polyvinyl compound, such as polyvinyl pyrrolidone, and a plasticizer. The composition layer secures the patch to the subject to allow for the topical administration of the medicinal agent to the subject. The patch of the present invention further includes a backing layer and an adhesive layer for securing the backing thereto. Other patch embodiments can include, if desired, a pharmaceutically acceptable diluent. The patch of the invention advantageously administers a medicinal agent to a mucous membrane or dermis of the subject in a relatively easy and non-invasive manner.

The present invention also provides a method for delivering a medicinal agent to the oral mucosa of a subject by way of a patch that includes the medicinal agent, a removable liner, and a composition layer that includes a therapeutically effective amount of the medicinal agent in admixture with a pharmaceutically acceptable polyvinyl pyrrolidone compound and a plasticizer.

The present invention further pertains to a packaged patch that also includes instructions for using the patch to deliver a medicinal agent to a subject.

## Brief Description of the Drawings

The foregoing and other objects, features and advantages of the invention will be apparent from the following description and apparent from the accompanying drawings, in which like reference characters refer to the same parts throughout the different views.

The drawings illustrate principles of the invention and, although not to scale, show relative dimensions.

Figure 1 is a cross-sectional view of the biological transdermal patch of the present invention.

**Description of Illustrated Embodiment**

The present invention pertains to a patch suitable for administering a medicinal agent to a subject that includes a removable liner forming a substrate, and a composition layer that includes a therapeutically effective amount of the medicinal agent in admixture with a pharmaceutically acceptable polyvinyl compound, such as polyvinyl pyrrolidone, and a plasticizer, to a subject to effect a biological change.

Figure 1 illustrates the patch 10 of the present invention. The illustrated patch includes a release liner 12 forming a substrate, a drug composition layer 14 that retains a medicinal agent, an adhesive layer 16, and a backing layer 18. These patch components form a stacked structure, as shown. Specifically, the release liner side 12A contacts an adjacent side 14A of the drug composition layer. The release liner 12 preferably mechanically supports the drug composition layer 14, and preferably functions as a pharmaceutically acceptable substrate during preparation of the drug layer.

For example, employing known pharmaceutical manufacturing techniques for transdermal and buccal patches, the drug composition layer 14 can be cast on the release liner 12 by preparing an aqueous or solvent slurry (mixture) containing selected compositions according to need. The slurry is then cast or spread onto the surface 12A of the liner 12 to coat the same. In an alternate embodiment, the composition layer can be separately cast and then joined with the release liner. The drug layer 14 can be formed from, in the wet stage, a selected medicinal agent, an adhesive or viscosity agent, a plasticizer and a solvent. If desired, one or more pharmaceutically acceptable diluents can be added to the slurry. The mixture is then allowed to dry according to known methods, such as air-drying, with or without heat, on the release liner to form a thin, flexible drug composition layer 14. In the illustrated dried form of the composition layer 14, the solvent preferably evaporates to form the final drug layer 14.

The backing layer 18 is then coated with a layer of adhesive 16 and laminated on the drug layer 14. The release liner 12, which can be any size suitable for manufacturing, is then diecut to form patches of the appropriate size. The patch 10 is then packaged, if desired, with suitable instructions. Those of ordinary skill will appreciate that the foregoing is a matrix-type batch process typically employed to form matrix-type patches. Also well known are techniques for forming reservoir-type and adhesive-type patches. Hence, although a matrix-type patch is shown, the teachings of the present invention can also be employed to form reservoir and adhesive type patches, are deemed to form part of the present disclosure.

Methods other than those described above and known to those of ordinary skill in the pharmaceutical preparation field can be employed to produce the drug composition layer 14 of the patch 10 of the present invention. For example, there can be employed a calendering method whereby the medicinal agent in admixture with one or more of the foregoing compounds is rolled between heated rollers to form a thin film or sheet.

In the illustrated patch 10, the adhesive layer 16 is disposed on the top side 14B of the drug composition layer, which is disposed opposite the release liner surface 12A. The adhesive layer can be any suitable, flexible, biologically compatible adhesive that properly and adequately secures the backing layer 18 to the drug composition layer 14.

The patch 10 is secured to the subject by removing the release liner 12 and by placing the exposed side, e.g., side 14A, of the drug composition layer 14 against a selected surface of the subject, such as the epidermis or mucosa, such as the oral mucosa. The backing layer 18 is thus disposed on the side of the patch opposite the surface of the intended site and is thus immediately and directly exposed to the surrounding environment. The backing 18 preferably limits the passage of the medicinal agent from the drug layer 14 into the surrounding environment. The backing layer 18 further operates to visually indicate the location of the patch when applied to the subject. The backing can be formed from any material suitable for use at the intended application site, as described further below. For example, the layer 18 can be formed of a colored material suitable for use as a visual indicator of the position of the patch 10.

According to a preferred practice of the present invention, the medicinal agent is present in the drug layer in an amount of from about 1% to about 70% and preferably 4% to 50% by weight, and the plasticizer is present in an amount of from about 1% to about 50% and preferably from about 5% to 20% by weight. The adhesive compound is preferably a polyvinyl compound, and most preferably is polyvinyl pyrrolidone, and is present in the drug layer in an amount of from about 5% to about 80% and preferably 5% to 50% by weight. If desired, the diluent can be present in an amount from about

5% to about 50% by weight. The foregoing measurements also may be characterized in terms of concentrations.

The term "suitable patch" or "patch" as used herein is intended to include any patch known to those of ordinary skill, such as transdermal, buccal or oral mucosa patches, that is capable of adhering or being affixed to the dermis, e.g., skin, buccal or mucosa of the subject. The patch typically includes a constituent component, e.g., the drug layer 14, that is capable of retaining and delivering the medicinal agent to the subject. Suitable materials for selected patch components (e.g., liners and backing) and designs of the patches are well known in the pharmaceutical and drug delivery art. Moreover, the size, shape and thickness of the patch can be changed to accommodate the exigencies of the particular situation, including the type of medicinal agent that is to be applied to the subject and the preferred application site, and are not particularly critical to the present invention.

The release liner 12 can be formed of any biologically compatible material that is easily and readily removable from the composition layer and, if desired, is suitable to function as a substrate during the formation of the drug composition layer. The release liner should also be compatible with the particular medicinal agent and the particular adhesive compound used. Examples of release liners include conventional release liners comprising a known sheet of natural or synthetic material such as webs of polyester, polyethylene, polystyrene, high density polyethylene (HDPE), polyethylene terephthalate (PET), or other polymers such as polypropylene or combinations of the foregoing, as well as other suitable materials such as polyester, polyvinyl films, or polyethylene-coated paper which can be coated with a suitable low-friction, easy release coating, e.g., silicon-type coating, such as that available under the trade designation Daubert 164Z from Daubert Co., or SCOTCHPAK brand 1022 film from 3M, as is known in the art. Typical release liners may also comprise double coated, differential release liners or the use of two single coated release liners, as is known in the art.

The backing layer 18 can be formed of any relatively flexible biologically compatible material that is suitable at least in part for use as a barrier to unwanted leakage of the medicinal agent therethrough and/or as a visual indicator of the location of the patch, and to protect the patch. The backing layer can be made of a sheet or film and may or may not contain pigment. The layer is preferably composed of material that mimics the contours of the application site with little or no likelihood that the patch will disengage from the subject due to the differences in the flexibility and resiliency of the site and the patch. Examples of the type of materials that can be used include metal foil, metallized plastic or one or more layers of natural or synthetic polymer materials, or of thin films including polyethylene and ethylene copolymers, ethylene methyl acrylate,

ethylene vinyl acetate, polypropylene, polyisobutylene including rubber-based compounds, styrene, styrene-butadiene, polystyrene, polyurethane, or a combination of different resins, acrylonitrile, cellulose acetate, polycarbonate, polyester, polyamides, randomly-oriented nylon fibers, rayon, polyvinylidene chloride, polyvinyl chloride, and gauze. The backing can also be a laminate of different materials comprising gauze or other suitable material and one or more of the foregoing polymers. As set forth above, the backing layer provides ease of handling and concomitantly functions as a visual indicator of the location of the patch.

The backing can also be suitably flexible to allow easy handling and placement at the intended site, and is preferably compatible with the adhesive layer and the constituents of the drug layer to ensure that the backing layer does not degrade the effectiveness of the drug composition layer and vice versa.

The release liner and backing layer can have any selected thickness, and preferably ranges between about 1 mil and about 20 mils.

The adhesive layer 16 can be any biologically compatible adhesive, such as a pressure sensitive adhesive, and preferably is composed of those adhesives that are suitable for use in the oral cavity of the subject. The adhesive can include those adhesives made of polyisobutylenes, polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether block amide copolymers (PEBAX copolymers), tacky rubbers such as polyisobutene, polystyrene-isoprene copolymers, polystyrene-butadiene copolymers, and mixtures thereof. The preferred adhesive includes acrylic resins, such as the product sold under the trade designation Gelva® by Monsanto, St. Louis, Missouri. Gelva is an acrylic resin solution that dries to a permanently tacky film, at room temperature.

The term "topical" or transmucosal administration/delivery is intended to include the direct administration of the patch and/or medicinal agent to the dermis or mucosal tissue or membrane of the subject, including the mucous membranes of the oral cavity of the subject, or any other location that is suitable for the administration of the medicinal agent. The term "oral mucosa" is intended to include all the mucous membranes of the oral or buccal cavity and which involve the alimentary canal, including the lining of the mouth, gums, and throat, as well as other mucosal membranes within the oral cavity of the subject including sublingual membranes and buccal (cheek) membranes. The oral mucosa preferably does not include the periodontal pocket formed in the gingiva of the patient.

The term "administering" is intended to include routes of administration which allow the medicinal agent and/or patch to perform its intended function of producing a

biological change in the subject. Examples of routes of administration which can be used include oral, transdermal, or transmucosal administration of the patch.

The term "medicinal agent" is intended to include any therapeutically effective agent that can be administered to the subject, such as by way of the dermis or mucosa, to effect a biological change. Examples of medicinal agents include, but are not limited to, local anesthetics, antimicrobial agents, anti-inflammatories, tranquilizers, vitamins, antihypertensive agents, analgesics, vasoconstrictors, vasodilators, muscle relaxants, and respiratory agents. Mixtures of two or more of the medicinal agents is also contemplated by the teachings of the present invention, as well as other agents not specifically set forth below, such as anorexics, antiarthritis, antiasthmatics, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, antimigraine preparations, antineoscants, antineoplastics, antipar Kinsonism drugs, antipsychotics, antispasmodics, antihypertensives, diuretics, cardiovascular preparations including beta-blockers and calcium channel blockers, central nervous system stimulants, immunosuppressives, steroids, sympathomimetics, antitumor agents, enzymes and herb medicines. According to a preferred practice, the patch includes a single medicinal agent, and preferably includes a single local anesthetic, such as lidocaine.

The term "local anesthetic" is intended to include amides and esters. Examples of the amides are lidocaine, prilocaine, mepivacaine, bupivacaine, dibucaine etidocaine. Esters include procaine, tetracaine, propoxycaine, chloroprocaine, benzocaine, butamben, picrate, cocaine, hexylcaine, piperocaine, oxyprocaine, proparacaine. Other suitable anesthetics include cyclomethycaine, dimethisoquin, ketocaine, diperodon, dyclonine and pramoxine, and other commercially known and available anesthetics.

The term "antimicrobial agents" is intended to include germicidal agents such as chlorohexidine, thimerosal, silver protein, chloramine, iodine glycerin, iodoform, boric acid, paraformaldehyde, phenol, hexylresorcinol, benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, phenododecium bromide, dequalinium chloride, cetylpyridinium chloride, and povidone iodine; antibacterial agents such as tetracycline, hydrochloride, penicillin, benzylpenicillin, ampicillin, carbenicillin, acetylkitasamycin, amoxicillin, bacitracin, cephalotin sodium, cephaloridine, cephalexin, erythromycin, chloramphenicol, oxytetracycline hydrochloride, doxycycline hydrochloride, polymyxin B sulfate, fradiomycin sulfate, and gentamicin sulfate; and antiviral agents such asidoxuridine, clarithromycin, and other anti-infectives including nitrofurazone, and the like, as well as antibiotics. Antibiotics are art-recognized and are chemical substances produced by microorganisms which suppress the growth of other microorganisms. However, the term as used herein is intended to include both naturally occurring and

chemically synthesized antibiotics. Examples of antibiotics include tetracycline, minocycline, doxycycline, vanomycin, erythromycin, penicillin, bacitracin, kanamycin, and neomycin.

The term "anti-inflammatories" is intended to include agents capable of reducing inflammation of a selected site, including inflammation of the oral mucosa (including the gum and supporting structures surrounding the teeth). The agents can be steroidal or non-steroidal, and can include indomethacin, eugenol, flubiprofen, ibuprofen, hydrocortisone, aspirin, salicylate acid, glycol salicylate, camphor, mefenamic, 1-menthol, fluphenamic acid, indomethacin, diclofenac, alclofenac, ketoprofen, naproxene, pranoprofen, fenoprofen, fentiazac, tolmetin, bendazac, bufexamac, piroxacam, phenylbutazone, antipyrine, meprizole, oxyphenbutazone, fenbufen, mefenamic acid, flurbiprofen, sodium, ketoprofen, tiaramid hydrochloride, benzydamine hydrochloride, ibufenac, perisoxalcitrate, indomethacin, aluminum flufenamate, thinoridine hydrochloride, clofezone, dexamethasone, triamcinolone acetonide, prostaglandin, and the like, as well as antihistaminic agents such as diphenhydramine hydrochloride, chlorpheniramine maleate, and clemastine, antibiotic agents such as sulfathiazole, sulfisomidine.

The term "tranquilizers" is intended to include reserpine, chlorpromazine, chlorpromazine, thiopropazate and antianxiety benzodiazepines such as alprozolam, chlordiazepoxide, clorazepate, halazepam, oxazepam, prazepam, clonazepam flurazepam, triazolam, lorazepam, diazepam, and the like.

The term "vasoconstrictors" is intended to include phenylephrine, naphazoline, and tetrahydrozoline.

Vitamins are art recognized and can include vitamins A, B, C, D, E and K and derivatives thereof.

The term "antihypertensive" agents is intended to include clonidine, α-methyldopa, reserpine, syrosingopine, rescinnamine, cinnarizine, hydrazine, prazosin, and the like.

The term "vasodilators" is intended to include amyl nitrite, butyl or isobutyl nitrites, sodium nitroprusside (SNP), S-nitroso-N-acetylpenicillamine, NaNO2, molsidomine, isosorbide dinitrate, and organic nitrates such as nitroglycerin, isosorbitol dinitrate, erythritol tetranitrate, and pentaerythritol tetranitrate, dipyridamole, dilazep, trapidil, trimetazidine, and the like.

The term "muscle relaxants" is intended to include tolperisone, baclofen, dantrolene sodium, and cyclobenzaprine.

The term "respiratory agents" is intended to include theophilline and $\beta_2$-adrenergic agonists, such as albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, tetroquinol, and the like.

The term "plasticizer" is intended to include any suitable composition that enables the finished, i.e., dried, composition to congeal into a suitable solid or semi-solid, e.g., soft film, composition layer that retains the medicinal agent and effects relatively easy administration of the medicinal agent to the subject at the selected application site. The plasticizer preferably does not interact with the medicinal agent so as to reduce or to degrade the effectiveness of the medicinal agent. Examples of the types of plasticizers include polyhydric alcohols including dipropylene glycol, propylene glycol, polyethylene glycol, glycerin, butylene hlycol, hexylene glycol, polyoxyethylene, polypropylene glycol, dipolypropylene glycol, sorbitol, ethylene glycol, diethylene glycol, triethylene glycol, and the like. Other suitable plasticizers include diethyl phthalate, dibutyl phthalate, butylphthalylbutyl glycolate, fatty acids such as oleic acid, linoleic acid, capric acid and the like, as well as fatty esters or alcohols. Still further plasticizers include triacetin.

The term "solvent" for use with the patch of the present invention includes pharmaceutically acceptable compositions that preferably do not adversely affect the effectiveness of the medicinal agent, affect the ability of the composition layer to adequately congeal, and/or affect the adhesion properties of the adhesive compound. The solvent can include water or organic solvents such as ethanol, isopropanol, acetone, herane, or other evaporable organic solvents. These of ordinary skill will be readily able to determine the approximate or suitable solvent by examining the individual components of the composition layer of the patch 10 of the present invention.

The term "diluent" suitable for use with the medicinal agent and the plasticizer of the composition layer of the present invention includes pharmaceutically acceptable substances that preferably do not adversely affect the effectiveness of the medicinal agent, affect the ability of the composition layer to adequately congeal on the liner portion of the patch, and/or affect the adhesion properties of the patch, e.g., the adhesive compound of the composition layer. The diluent can include polyhydric alcohols such as organic polyalcohol and includes dipropylene glycol, propylene glycol, polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polyoxyethylene polypropylene glycol, sorbitol, ethylene glycol, and the like. Other suitable diluents include fatty acids such as oleic acid, linoleic acid, capric acid and the like, as well as fatty esters or alcohols. Further diluents include pharmaceutical excipients, such as factose, sucrose, polysaccharides, cellulose, starch, talc, and other known excipients. Still further suitable diluents include other non-toxic, non-volatile solvents commonly used in dermal or

transdermal compositions for dissolving or diluting like compounds. The diluent selected for use with the present invention depends upon the particular medicinal agent and/or the plasticizer used.

The term "adhesive compound" is intended to include any non-toxic compound that becomes tacky or sticky or is capable of adhering to the subject upon the application of some minimum pressure or upon the application of water. More specifically, the compound is intended to include any substance, inorganic or organic, natural or synthetic, that is capable of surface attachment at an intended site. The adhesive compound can include any non-toxic polymers, particularly those polymers that can be used in conjunction with one or more of the medicinal agents of the present invention and can be used to carry in an admixture those agents for delivery to the dermis or oral mucosa. Examples of adhesive carriers suitable for use with the present invention can include natural or synthetic elastomers, such as polyisobutylene, styrene, butadiene, acrylics, styrene butadiene block copolymers, acrylic acid, polyacrylates, polyamides, polyesters, polyolefins, starch, gum arabic, natural and synthetic phospholipids such as cephalins and lecithins, and polysaccharides such as karaya gum, tragacanth gum, pectin, guar gum, xanthum gum, acacia, agar, alginic acid, aluminum monostearate, purified and unpurified bentonite and bentonite magma, cellulose, and cellulose derivatives, such as methyl cellulose, ethyl cellulose, hydroxypropylcellulose, hydroxyethyl cellulose, propyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose calcium and sodium carboxycellulose acetate and the like, as well as other substances suitable for use for transdermal or mucosal delivery including synthetic polymers such as polyvinyl compounds. The adhesive can be modified appropriately so as to adhere to the skin or mucosal tissue, depending on the intended application site. Other suitable compounds include art recognized and known viscosity agents.

The preferred compound of the present invention includes polyvinyl compounds. The term "polyvinyl adhesive compound" is intended to include polymers of vinyl monomers and are known in the art. Representative examples include polyvinyl ethers and resins such as vinyl and polyvinyl alcohol, including hydrolyzed or partially hydrolyzed polyvinyl alcohols, or copolymers thereof with vinyllaurate or maleic acid, polyvinyl esters, polypropylene, polybutylene, polyvinyl acetate or copolymers thereof, polyvinyl chloride, polyvinyl ethylether, polyvinyl pyrrolidone, polyacrylic acid, polymethacrylates including copolymers of methacrylic acid, styrene or a vinyl type ether monomer with acrylic acid and salts thereof.

The term "polyvinyl pyrrolidone" is the homo-polymer of 1-ethylenyl-2-pyrrolidinone, and is also known as 1-vinyl-2-pyrrolidinone polymer. A common name

for this chemical substance is povidone and the compound is sometimes designated as PVP. Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups which have been polymerized into polymer chains of various molecular weights, generally having mean molecular weights ranging from about 10,00 to 700,000 although polymers of both lesser and higher molecular weights are known.

Povidone is available as an article of commerce, either as a dry powder or in an aqueous solution for use in a wide variety of chemical, pharmaceutical and food manufacturing processes as well as special industrial compositions such as inks, paints and emulsions, cosmetics and germicidal products. Povidone is also used for example in the manufacture of adhesives to improve strength and toughness; in cosmetic products to condition and protect skin and hair; in pharmaceutical manufacture as a binder, coating agent, dispersant, adhesive (tacky when activated by water) protective colloid, and as a drug release controller for controlling the rate of release of the medicinal agent. Underriding the overall use of povidone in manufacture and formulation of different compositions is its contribution to the viscosity of the fluid medium being used. The viscosity contribution of povidone ranges from high viscosity to low viscosity and is a function of the average molecular weight of the polymer. Povidone is classified by constants, known as K-values, which are assigned to the various povidone polymers. These constants are derived from viscosity measurements in accord with the well known Fikentscher's formula and the smaller the K-value, the lower the intrinsic viscosity of the polymer.

The more common commercially available povidone polymers have K-values of K-14, K-30, K-60 and K-90, and in aqueous solutions, povidone K-15 and povidone K-30 have little effect on viscosity in concentrations below 10%, whereas povidone K-60 and povidone K-90 have considerable influence on the flow properties of a solution at such concentrations. While the viscosity effect of povidone is virtually unchanged by pH, concentrated hydrochloric acid and strong alkali have been shown to influence the viscosity of povidone. Moreover, certain organic solvents have a particular effect on the viscosity contribution of povidone, the intensity of which is related to the polarity of the particular organic solvent. Those of ordinary skill can determine without undue experimentation the proper viscosity from the commercially available povidone compounds that is suitable as forming part of the reservoir, e.g., drug layer 14, that contains the medicinal agent.

The language "pharmaceutically acceptable carrier" is intended to include substances capable of being combined with or coadministered with the compounds of the drug layer of the patch 10 of the present invention. Examples of such carriers include solutions, solvents, dispersion media, delay agents, emulsions and the like. The

use of such media for pharmaceutically active substances are well known in the art. Any other conventional carrier suitable for use with the medicinal agents also fall within the scope of the present invention.

The language " therapeutically effective amount" of the medicinal agent is that amount necessary or sufficient to cause or to initiate a biological change in the subject. The effective amount can vary depending on such factors as the amount and type of medicinal agent employed, the particular plasticizer and/or solvent, the size of the subject, the mode and site of administration, including the size of the patch, and the particular duration required to effect or maintain the biological change. For example, the choice of the medicinal agent can affect what constitutes an "effective amount". One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the medicinal agent without undue experimentation. The methodology set forth in the Examples below also can be used to determine an "effective amount." For example, one of ordinary skill would be able to ascertain the effective amount of a local anesthetic to be applied to the subject based on the Examples, the available literature, and known practices in the field.

The medicinal agents contained within the drug composition layer 14 of the patch 10 can be in different forms, such as uncharged molecules, components of molecular complexes or pharmacologically acceptable salts or derivatives thereof. Simple derivatives of the medicinal agents such as pharmaceutically acceptable ethers, esters, amides, and the like which have desirable retention and release characteristics but which are easily hydrolyzed at body pH, enzymes, pro-active forms and the like can be employed. The dosage or amount of the medicinal agent can be determined by one of ordinary skill, depending upon the application site, the medicinal agent, and the amount, type and duration of the desired biological change to be effected by application of the patch of the present invention.

As a general rule, in the preferred case of application of a local anesthetic to the oral mucosa of the subject by a patch, the concentration of the agent and the duration of application of the patch can be determined based upon the anesthetic's ability to penetrate and to be absorbed by the subject and to be at peak effectiveness and/or to retain a selected level of effectiveness within a selected range of time. This range preferably is between about 2 minutes and about 30 minutes, or even longer. Of course, the effectiveness and duration of the agent depends upon the particular type of agent. Longer or shorter durations of effectiveness can also be selected dependent on need, as will be appreciated by the ordinarily skilled artisan. Furthermore, these same factors apply to application of the patch at sites other than the oral mucosa.

The term "onset of anesthesia" is intended to mean the time in which it takes the anesthesia (such as the local anesthetic) to initially effect a biological change in the subject. This onset time varies depending upon the application site, the quantity of the anesthesia, and the mode of application. The term "duration of anesthesia" is intended to mean the total time that the anesthetic is capable of producing the biological change. For example, the duration can be the total time in which the anesthetic blocks nerve conduction. The foregoing depends upon all the factors listed for the onset of anesthesia. In general the relative speed of the onset of anesthesia and the duration of anesthesia for any given anesthetic is available in the literature or can be readily and easily determined by one of ordinary skill without undue experimentation.

The term "subject" is intended to include humans, dogs, cats, pigs, cows, horses, rats, and mice.

The present invention further pertains to a packaged patch that contains either an adhesive compound or a polyvinyl compound, such as polyvinyl pyrrolidone, and a local anesthetic (medicinal agent) as described above, packaged with instructions for using the patch to effect a biological change, e.g., induce anesthesia to block nerve conduction. The instructions would provide such information as the manner in which to clean the application site, the manner of use and application of the patch, and the preferred application time.

A significant advantage of the present invention is that it provides for a patch that can be applied to the dermis or mucosal surface. According to one preferred practice, the patch includes an anesthetic that can be used in a variety of medical settings. The patch thus provides an easy, non-invasive method of administering an anesthetic to the mucosal surface of a subject.

Other advantages of the patch of the present invention include a reduction in infections that may develop from injections. Also, the patch is relatively inexpensive alternative to the use of needles.

The following invention is further illustrated by the following examples, which should not be construed as further limiting. The contents of all references, pending patent applications and published patents, cited throughout this application are hereby expressly incorporated by reference.

## *EXAMPLES*

### Example 1

The drug composition layer of the patch of the present invention is first formed by mixing together 20.27% by weight of a single local anesthetic such as lidocaine,

18.4% by weight povidone, 6.34% by weight glycerin, and 55% by weight 190 proof alcohol. This mixture is then coated on a polyethylene release liner, e.g., a polyester support mat. The mixture is then dried.

When dried, the alcohol evaporates and the remaining components of the drug mixture as present in the following quantities: 45% by weight lidocaine, 14% by weight glycerin, and 41% by weight povidone.

The drug layer formed on the release layer is then laminated to a backing layer that is coated with a suitable adhesive. The backing layer is formed of either polyethylene, polypropylene, polyurethane or a combination of resins. Alternatively, gauge or other suitable material can be laminated together with the polymer layer for a better appearance and ease in handling. The adhesive can be an acrylic resin such as that sold under the tradename Gelva® Multipolymer Solution 737, manufactured by Monsanto, St. Louis, Missouri, U.S.A. The adhesive layer formed on the backing contacts the exposed surface of the drug layer formed on the liner. This adhesive dries to a permanently tacky film at room temperature.

In use, the release liner is peeled from the patch and the patch is placed within the oral or buccal cavity of a subject at the intended application site. The patch adheres to the mucosa surface upon contact therewith.

The anesthetic onset time starts at about 5 minutes after placement at the intended site. The patch can be left on the mucosal surface for as long as 2 hours, and even longer, depending upon the thickness of the drug composition layer and the dose of the anesthetic. According to one practice, the lidocaine content can vary between about 10 mg-20 mg per patch. The drug is released from the patch in a slow controlled manner. For a faster onset time, the patch can be removed from the mucosal surface about 5 minutes after application.

The drug residue left on the mucosal surface can be cleaned anytime after use to avoid subjecting the subject to unnecessary anesthesia.

**Example 2**

The drug composition layer of the patch of the present invention is first formed by mixing together lidocaine, povidone, glycerin, a solvent such as alcohol and a suitable diluent. This mixture is then coated on a polyethylene release liner, e.g., a polyester support mat. The mixture is then dried.

When dried, the alcohol and if desired, the diluent, evaporates.

The drug layer formed on the release layer is then laminated to a backing layer that is coated with a suitable adhesive. The backing layer is formed of either polyethylene, polypropylene, polyurethan or a combination of resins. Alternatively,

gauge or other suitable material can be laminated together with the polymer layer for a better appearance and ease in handling. The adhesive can be an acrylic resin such as that sold under the tradename Gelva® Multipolymer Solution 737, manufactured by Monsanto, St. Louis, Missouri, U.S.A. The adhesive layer formed on the backing contacts the exposed surface of the drug layer formed on the liner. This adhesive dries to a permanently tacky film at room temperature.

In use, the release liner is peeled from the patch and the patch is placed within the oral or buccal cavity of a subject at the intended application site. The patch adheres to the mucosa surface upon contact therewith.

The anesthetic onset time starts at about 5 minutes after placement at the intended site. The patch can be left on the mucosal surface for as long as 2 hours, and even longer, depending upon the thickness of the drug composition layer and the dose of an anesthetic. According to one practice, the lidocaine content can vary between about 10 mg-20 mg per patch. The drug is released from the patch in a slow controlled manner. For a faster onset time, the patch can be removed from the mucosal surface about 5 minutes after application.

## EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

Claims:

1. A patch suitable for topically administering a medicinal agent to a subject, comprising

a backing layer which includes visual indication means for indicating the relative location of the patch, and

a composition layer formed on said backing, said composition layer including a therapeutically effective amount of the medicinal agent in admixture with a pharmaceutically acceptable polyvinyl pyrrolidone compound and a plasticizer.

2. The patch of claim 1 further including
a removable liner, and
adhesive means for securing said backing to a side of said composition layer opposite said removable liner.

3. The patch of claim 2 wherein said adhesive means includes an acrylic resin.

4. The patch of claim 2 wherein said backing layer includes one of polyethylene and gauze.

5. The patch of claim 2 wherein said liner is composed of polyethylene.

6. The patch of claim 1 wherein said medicinal agent is selected from the group consisting of a local anesthetic, antimicrobial treatment, anti-inflammatory, tranquilizer, vitamin, antihypertensive agent, analgesic, vasoconstrictor, vasodilator, tranquilizer, muscle relaxant, and respiratory agent.

7. The patch of claim 1 wherein said medicinal agent is a local anesthetic.

8. The patch of claim 1 wherein said medicinal agent is lidocaine.

9. The patch of claim 1 wherein the plasticizer includes a polyhydric alcohol.

10. The patch of claim 1 wherein the plasticizer is glycerin.

11. The patch of claim 1 wherein said medicinal agent is present in said composition in an amount of from about 1% to about 70% by weight, said plasticizer is present in said composition in an amount of from about 1% to about 50%, and said polyvinyl pyrrolidone is present in said composition in an amount of from about 5% to about 80%.

12. The patch of claim 1 wherein said composition layer further includes a diluent.

13. The patch of claim 1 wherein said composition layer further includes a solvent.

14. An anesthetic patch for applying a local anesthetic to the oral mucosa of a subject, comprising

a backing layer which includes visual indication means for indicating the relative location of the patch, and

a composition layer disposed on said backing layer, said composition layer including a therapeutical effective amount of the local anesthetic in admixture with a polyvinyl pyrrolidone compound and a plasticizer.

15. The anesthetic patch of claim 14 further including
a removable liner, and
adhesive means for securing said backing to a side of said composition layer opposite said liner.

16. The anesthetic patch of claim 15 wherein said adhesive means includes an acrylic resin.

17. The anesthetic patch of claim 15 wherein said backing layer includes one of polyethylene and gauze.

18. The anesthetic patch of claim 14 wherein said local anesthetic is lidocaine.

19. The anesthetic patch of claim 14 wherein the plasticizer includes a polyhydric alcohol.

20. The anesthetic patch of claim 14 wherein said local anesthetic is present in said composition in an amount of from about 1% to about 70% by weight, said plasticizer is

present in said composition in an amount of from about 1% to about 50%, and said polyvinyl pyrrolidone is present in said composition in an amount of from about 5% to about 80%.

21. The anesthetic patch of claim 14 wherein said composition layer further includes a diluent.

22. A method for topically delivering a medicinal agent to a subject, comprising providing a patch containing the medicinal agent, said patch including a backing layer which includes visual indication means for indicating the relative location of the patch and a composition layer having a tissue-engaging surface disposed on said backing, said composition layer including a therapeutically effective amount of the medicinal agent and a pharmaceutically acceptable polyvinyl pyrrolidone compound and a plasticizer, and

placing the tissue-engaging surface in contact with the subject to deliver the medicinal agent thereto, such that the relative location of the patch is indicated by the visual indication means.

23. The method of claim 22 wherein said medicinal agent is selected from the group consisting of a local anesthetic, antimicrobial treatment, anti-inflammatory, tranquilizer, vitamin, antihypertensive agent, analgesic, vasoconstrictor, vasodilator, tranquilizer, muscle relaxant, and respiratory agent.

24. The method of claim 22 wherein said medicinal agent is a local anesthetic.

25. The method of claim 22 wherein said medicinal agent is lidocaine.

26. The method of claim 22 wherein said composition layer further includes a diluent.

27. The method of claim 22 wherein said medicinal agent is present in said composition in an amount of from about 1% to about 70% by weight, said plasticizer is present in said composition in an amount of from about 1% to about 50%, and said polyvinyl pyrrolidone is present in said composition in an amount of from about 5% to about 80%.

28. A sustained release delivery system for site-specific delivery of a medicinal agent to the oral mucosa of a subject, comprising

a backing layer which includes visual indication means for indicating the relative location of the patch,

a composition layer formed on said backing, said composition layer including a therapeutically effective amount of the medicinal agent in admixture with a pharmaceutically acceptable polyvinyl pyrrolidone compound, and a plasticizer.

29. The system of claim 128 wherein said medicinal agent is a local anesthetic.

30. A packaged sustained release delivery system for applying a medicinal agent to the oral mucosa of a subject, comprising

a patch containing a backing layer which includes visual indication means for indicating the relative location of the patch, and a composition layer formed on said backing, said composition layer including a therapeutically effective amount of the medicinal agent in admixture with a pharmaceutically acceptable polyvinyl pyrrolidone compound, and a plasticizer, and

instructions for using the delivery system for applying the medicinal agent to the oral mucosa of the subject.

31. The packaged system of claim 30 wherein said medicinal agent is a local anesthetic.

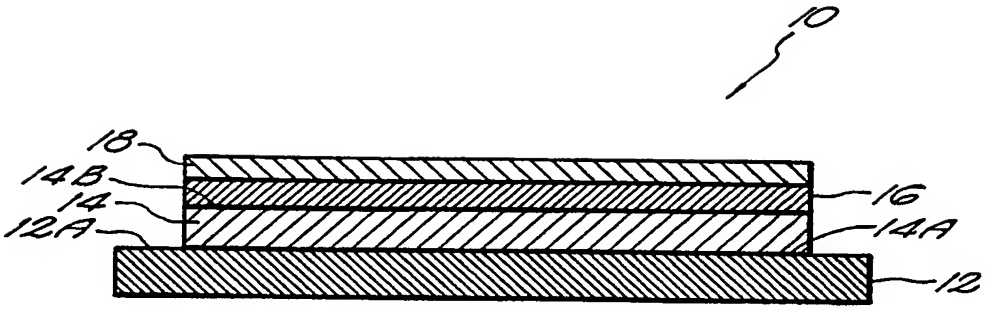


FIG. 1

# INTERNATIONAL SEARCH REPORT

Int[illegible]ional Application No
PCT/US 97/19663

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/70

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 89 10740 A (INNOVATA BIOMED LTD) 16 November 1989<br><br>see abstract<br>see page 2, line 22 - page 4, line 2<br>see page 4, line 33 - page 5, line 1<br>see page 5, line 21-36<br>see page 6, line 15-16<br>see page 6, line 31 - page 7, line 3<br>see tables 1,2<br>see claims<br>---<br>-/-- | 1-3,<br>6-11,<br>13-16,<br>19,20,<br>22-25,<br>27-31 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 March 1998 | 02/04/1998 |

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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | La Gaetana, R |

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Int tional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | GB 1 108 837 A (ASTRA PHARMACEUTICAL PRODUCTS) 3 April 1968<br><br>see page 1, line 12-15<br>see page 2, line 5-15<br>see page 2, line 63-93<br>see page 3, line 66-70<br>see examples 10,14,17<br>see claims 3,5,7,8 | 1,2,<br>6-15,<br>18-31 |
| X | US 5 120 546 A (HANSEN JENS ET AL) 9 June 1992<br><br>see column 5, line 16-24<br>see column 5, line 34-50<br>see column 6, line 45<br>see column 8, line 26<br>see column 8, line 47 - column 9, line 7<br>see column 9, line 39-43<br>see column 9, line 59<br>see column 9, line 66-67<br>see column 10, line 17-23<br>see column 10, line 31-50<br>see examples 3,4<br>see claims 4,7 | 1-9,<br>13-16,<br>18,19,<br>21-26,<br>28-31 |
| A | US 5 460 620 A (SMITH JAMES A ET AL) 24 October 1995<br>see column 6, line 6-10<br>see column 7, line 4-6<br>see column 13, line 7-9<br>see column 23, line 38<br>see claims 1,10,12,15,16 | 4 |

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 97/19663

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 8910740 A | 16-11-89 | NONE | |
| GB 1108837 A | | BE 690383 A | 29-05-67 |
| | | DE 1617282 A | 06-02-75 |
| | | DK 118841 B | 12-10-70 |
| | | FR 6733 M | 24-02-69 |
| | | LU 52460 A | 25-06-68 |
| | | NL 6616878 A | 31-05-67 |
| US 5120546 A | 09-06-92 | AT 137405 T | 15-05-96 |
| | | AU 6973591 A | 24-07-91 |
| | | DE 69026837 D | 05-06-96 |
| | | DE 69026837 T | 02-01-97 |
| | | EP 0519926 A | 30-12-92 |
| | | ES 2086529 T | 01-07-96 |
| | | JP 5504895 T | 29-07-93 |
| | | WO 9109592 A | 11-07-91 |
| US 5460620 A | 24-10-95 | US 5242433 A | 07-09-93 |
| | | CA 2151122 A | 23-06-94 |
| | | EP 0746377 A | 11-12-96 |
| | | WO 9413354 A | 23-06-94 |
| | | US 5470323 A | 28-11-95 |
| | | US 5476962 A | 19-12-95 |
| | | US 5616745 A | 01-04-97 |